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Preparation and evaluation of bioadhesive benzocaine gels for enhanced local anesthetic effects

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Abstract

This study was performed to develop new enhanced anesthetic benzocaine gels with a suitable bioadhesive property for local anesthetic effects. As the concentration of benzocaine in the HPMC gels increased up to 15%, the permeation of drug increased, thereafter slightly increased. The activation energy of drug permeation was 11.29 kcal/mol. Bioadhesive forces were also measured. The permeation rate of drug through the skin was studied using various enhancers, such as glycols, non-ionic surfactants or fatty acids. Among the enhancers used, diethylene glycol showed the most enhancing effects. Analgesic activity was examined using a tail-flick analgesimeter. According to the rat tail-flick test, the value of $AUEC_{0-360\,min}$ of 15% benzocaine gels containing diethylene glycol was 4662 ± 200 s min, while that of gels without diethylene glycol was 3353 ± 132 s min, showing about 1.39-fold increase in analgesic activity. Fifteen percentage of benzocaine gels containing diethylene glycol showed the most enhanced, prolonged analgesic effects, showing the maximum anesthetic effects at 240 min, while the gels without diethylene glycol showed maximum effect at 180 min.

Keywords: Local anesthetics; Benzocaine; Permeation; Enhancer; Tail flick

Benzocaine, one of the ester type of long acting, local anesthetics, has been used for the relief of local pain. Of the many drug delivery systems, transdermal drug delivery has some advantages of controlled delivery of the drug for an extended period of time. In the case of application of ointments, solutions and lotions onto dermal tissues, it is difficult to expect their effect for a significant period of time, because wetting, temperature, movement, etc. easily remove them. New formulations with suitable adhesion which show sustained effects are required (Ch'ng et al., 1985). Percutaneous administration of bioadhesive gels allows ready application and ease of removal. The use of penetration enhancers such as bile salts, surfactants, chelators, fatty acids and their derivatives can be important (Angust and Rogers, 1989; Shin et al., 1999, 2000).

The purpose of this study was to develop an enhanced anesthetic benzocaine gel containing an enhancer by studying its in vitro permeation characteristics and in vitro performance using the tail-flick analgesic test.

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1. Measurement of bioadhesive forces of the HPMC gels containing benzocaine

Three kinds of HPMC (K4M, K15M, and K100M) were used in this study. Two grams of hydroxypropyl methylcellulose (HPMC) was dissolved in water to make 70 ml. Thirty milliliters of 50% benzocaine solution in ethanol was added with vigorous stirring to the above polymer solution.

To evaluate the bioadhesive polymers, rat intestines (Tur and Ch'ng, 1998; Blanco-Fuente et al., 1996) were used. Adhesive forces were determined by measuring the maximum detachment force using an Auto Peeling Tester (C.K. Trading Co., South Korea). Cyanoacrylate adhesive was used to fix the intestine mucosa of rats to both the upper and lower supports. The HPMC gels were placed on the mucosa attached to both the supports (contact surface area, 0.5 cm^2). After attaching the gel to the intestinal mucosa, the force (contact pressure, 50 gf) was applied for 5 min. The determination of the detachment forces was carried out at a speed of 150 mm/min until the complete detachment of the components was achieved. The force required to completely separate the two compartments was recorded as the adhesion force, which was designated as gram force (gf).

2. Release of benzocaine from the hydroxypropyl methylcellulose gels

The in vitro release of drug from the HPMC gels was examined using the modified Keshary-Chien diffusion cell. The diameter of the cell was 1.5 cm, providing 1.77 cm^2 effective constant area and the volume of receptor chamber was 7 ml. The release test of benzocaine gels (0.5 g) was carried out with 40% PPG/PBS as a receptor medium. The receptor was maintained at 37 °C with circulating water jacket and stirred constantly at 350 rpm. The samples were taken from the receptor side at a predetermined interval and analyzed by UV-Vis spectrophotometer at 284 nm. The effects of drug loading dose on release from the gels were studied at drug concentrations of 5, 10, 15, and 20% (w/w), and the effects of temperature on drug release were studied at 28, 32, 37, and 42 °C.

3. Effects of an enhancer on the permeation of drug from the gels through rat skin

The diffusion studies through rat skin were carried out at 37 ± 0.5 °C. The freshly excised full-thickness rat skin was mounted on the diffusion cell with a diffusion area of 1.77 cm^2. Gels (5000) containing drug (15%) and enhancer (5%) were loaded onto the diffusion cell. The enhancers used were fatty acids (lauric acid, myristic acid, and capric acid) and glycols (diethylene glycol and tetraethylene glycol) and non-ionic surfactants (polyoxyethylene 2-oleyl ether, polyoxyethylene 2-stearyl ether, and polyoxyethylene 23-lauryl ether).

The effects of the penetration enhancers on the permeation rate of benzocaine were determined by comparing the flux of drugs in the presence and absence of enhancers, and defined as an enhancement factor (EF), (drug flux from the gels containing enhancer)/(drug flux from the gels without enhancer).

3.1. Tail-flick analgesic test

The bioadhesive benzocaine gels containing diethylene glycol as a penetration enhancer were formulated and the anesthetic effects of the gels were evaluated by the tail-flick analgesic test. A rat (Sprague–Dawley) was fixed on a tail-flick analgesimeter with a portion of the tail, 10 cm from its tip, exposed to heat from a projector lamp. A single control switch simultaneously activated the light and a timer. The timer stops automatically when the exposed rat's tail flicks. The time interval between switching on the light and flick of the tail was recorded. A 30 s cut-off time was used to avoid thermal injury. Benzocaine gels (50 mg) were covered at the root of the tail on midline. Tail-flick test was started 30 min after local application of gels, and the test was done every 30 min for 6 h.

4. Results and discussion

4.1. Release of benzocaine from the HPMC gels

The bioadhesive forces of K4M, K15M, and K100M HPMC gels at 2% concentration were 85.1 ± 11.6 gf, 114.2 ± 7.2 gf, and 134.3 ± 2.8 gf, respectively. From these results, HPMC-K100M which

showed the best bioadhesive force was chosen for the next studies. To establish the optimal conditions of the benzocaine gels, the effects of the loading dose on drug release were studied from the prepared 2% HPMC gels at $37 \pm 0.5\,^{\circ}C$. The drug concentrations tested were 5, 10, 15, and 20%, respectively. As the concentration of benzocaine in the gels increased up to 15%, the permeation of drug increased, and thereafter slightly increased. Therefore, the drug concentration in the gels was fixed at 15%. The effects of temperature of surrounding solutions on drug release from the 15% benzocaine gels were evaluated at temperatures of 28, 32, 37 and 42 °C. It should be noted that benzocaine release at 42 °C was increased to about 6.9-fold comparing with that at 28 °C. The higher the temperature, the greater the drug release, but for the practical use, a temperature of 37 °C was chosen. The apparent permeation coefficient increased, as the temperature of systems increased. The relationship between the permeation coefficient and the temperature is as follows:

$$P = P_0\, e^{-Ea/RT}$$

The logarithm of permeation coefficient is plotted as a function of the reciprocal of temperature and the slope calculated from the linear portion of plot was used to calculate the activation energy (Fig. 1). The activation energy for drug permeation of benzocaine was 11.29 kcal/mol. The observation indicates clearly that the release of drug from the gels is an energy-linked process (Miyazaki et al., 1984). The increased release with increasing temperature suggests that release characteristics of drug from the gels would change over the body temperature range. These findings indicate that special precautions should be taken with regard to monitoring body temperature in practical applications.

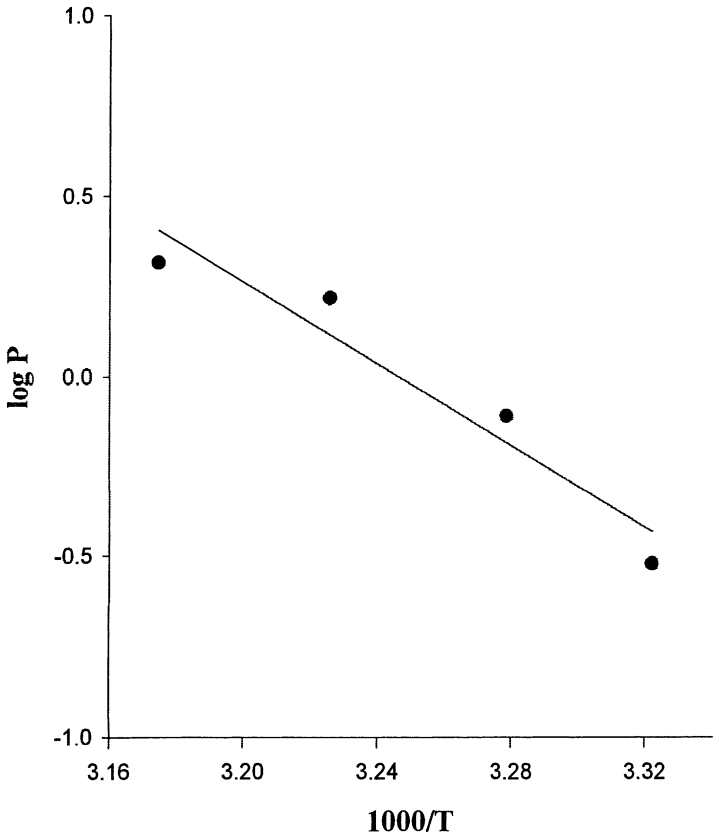

Fig. 1. Permeation coefficients of benzocaine from 15% benzocaine gels as a function of temperature (K).

Table 1
Enhancing factor of enhancers

Enhancer	Flux ($ug/cm^2/h$)	Enhancement factor
Control	41.55 ± 4.2	1.00
Tetraethylene glycol	62.53 ± 5.4	1.51
Diethylene glycol	77.24 ± 6.7	1.86
Polyoxyethylene 2-stearyl ether	70.26 ± 6.9	1.69
Polyoxyethylene 23-lauryl ether	50.43 ± 5.5	1.21
Polyoxyethylene 2-oleyl ether	74.55 ± 7.2	1.79
Lauric acid	70.68 ± 6.8	1.70
Myristic acid	52.30 ± 4.5	1.26
Capric acid	70.94 ± 6.6	1.70

4.2. Permeation of benzocaine from the gel containing various enhancers through rat skin

The effects of various enhancers on the percutaneous permeation of benzocaine were studied using rat skin (Table 1). Among the permeation enhancers tested, diethylene glycol showed the most effect, all possibly increasing the lipid fluidity of skins (Shin et al., 1999).

4.3. Tail-flick analgesic test of benzocaine gels containing an enhancer

In percutaneous permeation studies, gels containing diethylene glycol showed the best enhancing effects and were used for the rat tail-flick analgesic test. The value of $AUEC_{0–360\,min}$ (Area Under the Efficacy Curve) of benzocaine gels containing diethylene glycol was 4662±200 s min, while it was 3353±132 s min in the absence of enhancers. The efficacy of benzocaine gels containing diethylene glycol was four-fold greater than that without diethylene glycol. From the rat tail-flick test (Fig. 2), 15% benzocaine gels containing diethylene glycol showed the most enhanced,

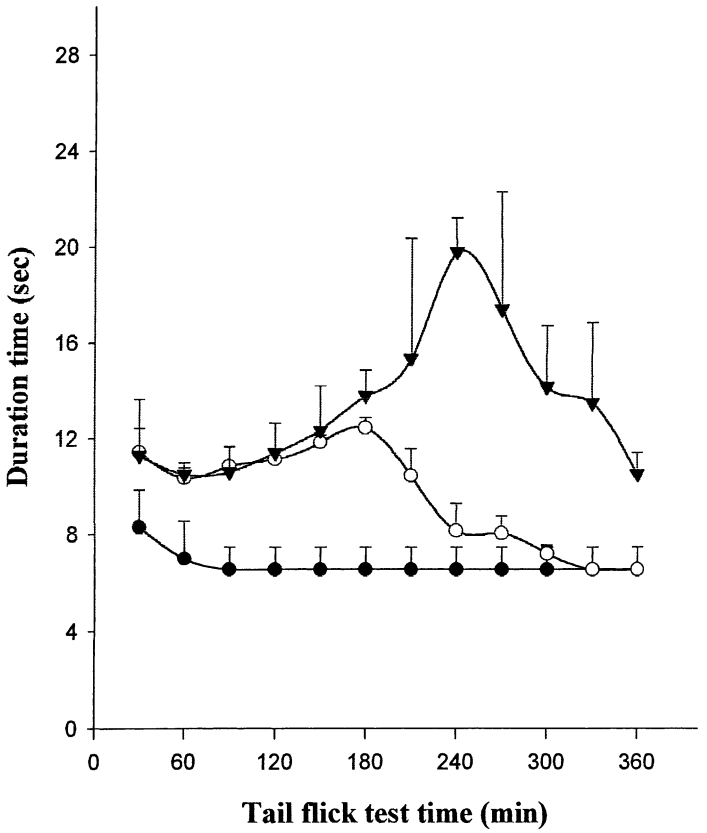

Fig. 2. Tail-flick test of 3% and 15% benzocaine gels ($n = 3$). Key: (●), control gels without benzocaine and diethylene glycol; (○), 15% benzocaine gels without diethylene glycol; (▼), 15% benzocaine gels containing diethylene glycol.

prolonged analgesic effects, showing a maximum anesthetic effect at 240 min, while the gels without diethylene glycol showed a maximum at 180 min.

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References

Angust, B.J., Rogers, N.J., 1989. Comparison of the effects of various transmucosal absorption promoters on buccal insulin delivery. Int. J. Pharm. 53, 227–235.

Blanco-Fuente, H., Anguiano-Iga, S., Otero-Espinar, F.J., Blanco-Mendez, J., 1996. In-vitro bioadhesion of carbopol hydrogels. Int. J. Pharm. 142, 169–174.

Ch'ng, H.S., Park, H., Kelly, P., Robinson, J.R., 1985. Bioadhesive polymers as platform for oral controlled delivery. J. Pharm. Sci. 74, 399–405.

Miyazaki, S., Takeuchi, S., Yokouchi, C., Takada, M., 1984. Pluronic F-127 gels as a vehicle for topical administration of anticancer agents. Chem. Pharm. Bull. 32, 4205–4208.

Shin, S.C., Cho, C.W., Choi, H.K., 1999. Permeation of piroxicam from the poloxamer gels. Drug Dev. Ind. Pharm. 25, 1273–1278.

Shin, S.C., Kim, J.Y., Oh, I.J., 2000. Mucoadhesive and physicochemical characterization of carbopol-poloxamer gels containing triamcinolone acetonide. Drug Dev. Ind. Pharm. 26, 307–312.

Tur, K.M., Ch'ng, H.S., 1998. Evaluation of possible mechanism of bioadhesion. Int. J. Pharm. 160, 61–74.